uable, yet, after a score of years, it must be conceded that not a few of the suggestions, which were most unsatisfactory at the time, have proved to be of lasting value. As if these occupations were not enough, he made frequent field studies, delivered many addresses and lectured to the college classes. Such unceasing toil told even on his extraordinary constitution; several times he was compelled to abandon everything abruptly at the close of the winter's work and to flee to Switzerland, where, with Desor and other friends, he would spend two months of absolute freedom from all care—but only to return to work at the same terrific pace, to make ready for another collapse.

The hundred volumes of reports giving the results of the Second Survey are his monument. He gathered around him a group of earnest workers into whom his own spirit was infused; in most instances he gave them free scope and was repaid by honest investigation. At the close of the survey work he undertook to prepare a final report; but the close application, which he deemed necessary, brought on the final break after he had completed the report up to the end of the Lower Carboniferous. In this marvelous compilation he gave a synopsis of every assistant's work, according unreserved recognition to each observer and frequently showing an unselfish neglect of credit due to himself for earlier discovery of facts and determination of principles.

Keen in perception, quick in comprehension, Professor Lesley at times reached conclusions too hastily, but no man was quicker than he to acknowledge an error. His broad reading and tenacious memory made him a well-furnished scholar; his cheery disposition made him an attractive companion. He knew little of the world and cared less for it; he was a typical student, who in worldly matters never outgrew his college days. Honest and true, he never remembered an injury, he never forgot a kindness. His faults were those of a whole-souled generous man.

For ten years Professor Lesley was laid aside from all labor, but he bore his affliction with more than patience and at last he passed away peacefully, without suffering, literally crossing the threshold in sleep.

In 1849 Professor Lesley married Susan I. Lyman, of Northampton, Mass., who, with two daughters, survives him.

JOHN J. STEVENSON.

*AN ASPECT OF MODERN PATHOLOGY.**

IT is a truism to assert that the great progress made in pathology during the past century is the result of the study of cellular structure and activity. The close of the nineteenth century has witnessed no lessening of the interest of pursuit of this study; but it has seen arise an endeavor to penetrate more deeply into the nature and properties of cells through which their manifold activities are brought about. Armed with a rich harvest of facts and methods supplied by physiological chemistry, investigators have attacked the question of the internal constitution of the cell with renewed vigor, and the degree of success of this effort is indicated by the strides made within the past two decades in unraveling the phenomena of immunity and allied states. The twentieth century has received from its predecessor a rich heritage of facts and principles relating to the intimate structure and function of cells, which is destined to yield a fruitage of great importance to physiology, pathology and practical medicine

I find myself in the enviable attitude of dealing with certain topics in experimental

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pathology, of recent acquisition and somewhat obscure nature, possessed by the assurance that my audience can afford to dispense with an explanatory introduction because of its acquaintance with the newer facts of immunity in relation to pathology, so brilliantly dealt with in Professor Welch's Huxley lecture.

So many pathological phenomena have, in the past, been attributed to alterations of the blood, and recent discovery has added so largely to the list of the activities of this fluid, that one is tempted, as he views the wonderful properties with which it is endowed, to exclaim with Goethe: 'Das Blut ist ein ganz besonderes Saft.' The manner of the solution of blood corpuscles brought about by alien serum is a well-known phenomenon that many years since, through the studies of Landois and others, was made to explain the unsuccessful and even disastrous effects of blood transfusion. More recent investigations have shown that by a process akin to artificial immunization to bacteria, a similar but more intense capacity of bringing about solution of blood corpuscles can be developed in blood serums which naturally do not possess this action, and increase of the power can be produced in serums in which it is already present.

This solution consists in the liberation of hæmoglobin from the stroma of red corpuscles and its diffusion through the fluid, a process to which the name 'hæmolysis' has been given. Careful observation of this phenomenon has shown that, in many cases, a state of coalescence of the corpuscles, to which the name 'agglutination' is applied, precedes that of solution; and, further, that while these changes are often associated, yet one may occur in the absence of the other.

While, under normal conditions, the serum of an animal is without injurious action upon the corpuscles suspended in it, yet in certain pathological states the serum suffers an alteration through which its corpuscles are acted upon injuriously, are made to agglutinate, and even to undergo complete dissolution. Coincident with the appearance of this activity, it often happens that the serum has acquired increased power of solution over corpuscles of a foreign nature; and this alteration in properties acquired by the serum is held responsible for the blood destruction that accompanies many of the infectious diseases, and is so apparent and serious a condition in certain diseases—*e. g.*, severe anæmias, the causation of which is still unknown.

In view of the acquisition of such new and hurtful qualities by the blood serum, the discovery in cultures of many kinds of pathogenic bacteria of hæmolytic and agglutinating substances for red corpuscles is a peculiarly welcome addition to our knowledge of blood destruction in disease. And while this knowledge has not led to the understanding of all forms of blood destruction, and has as yet failed to shed important light upon certain clinical types of severe and pernicious anæmia, we have obtained a new standpoint from which to view the so-called blood diseases that promises further progress in the near future.

It is common experience in science to find that accurate observation has preceded adequate explanation. The manner of action of bacterial agents upon red corpuscles, and our recently acquired knowledge of agglutination of cells in general, could not fail to suggest that certain kinds of thrombi are produced by a form of coalescence of corpuscles; and I was not, therefore, surprised to find unmistakable evidences of agglutination of red corpuscles in the blood vessels of the intestine and other organs in typhoid fever, in the lung in lobular pneumonia, and in some other

pathological conditions in man. That a similar form of thrombosis plays an important part in experimental pathology could be shown by studying the 'clots' formed in the heart and great vessels in poisoning by ether, alien serum and ricin injections in rabbits, and has been proved by the observations made by Fisher, working in Dr. Welch's laboratory, of the occurrence of such thrombi in experimental infections with the typhoid bacillus, and Boxmeyer, of Boston, of their existence in relation with certain necrotic foci in the liver in experimental hog-cholera bacillus infections. Heüter and Klebs and Welch had, many years ago, drawn attention to the fact that certain of the so-called hyaline thrombi appeared to be composed of fused and altered red corpuscles, observations which are confirmed and explained by these later findings.

It seems to me highly probable that agglutinative thrombosis will, in the near future, be recognized as an important pathological condition in man, and that a large number of the thrombi that arise in the course of infectious disease and, doubtless, diseases of uncertain etiology, will be discovered to have originated in agglutination. Not only will capillary hyaline thrombi be explained upon this basis, but the thrombi of larger vessels, such as those of the femoral vein, may equally be shown to have this mode of origin. I wish, in this connection, to draw attention to the unsatisfactory nature of the data relating to the mycotic origin of thrombi with which French writers especially have identified themselves, and to suggest that in agglutination a more adequate cause for thrombosis might come to be found.

The experimental study of agglutination seems capable of shedding much needed light upon the subject of intravascular clotting in general. I have been able to show that the so-called coagula which appear in the heart in experimental ether and alien serum poisoning are not clots in a true sense, but merely masses of fused red corpuscles; and Ehrlich many years ago endeavored to explain the lesions of experimental ricin poisoning upon the basis of his findings of capillary thrombi composed of agglutinated corpuscles. Ehrlich's attention was called to this appearance by the previous observations of Kobert and Stillmark upon the precipitating and coagulating effects of ricin upon red corpuscles *in vitro;* but the entire series of pathological effects of ricin upon the organism can not, as I pointed out some years ago, be explained by thrombosis.

That relation exists between extensive blood destruction and agglutinative thrombosis, the mode of action of ether and alien serum injections in producing rapid death quickly proves; and the essential identity of the agglutination produced *in vitro* and in the body by agglutinating and hæmolytic substances can be easily shown. If a dog or a rabbit is injected with a fatal quantity of hæmolytic serum and the gelatinized blood in the heart and great veins be removed and subjected to immediate examination in the fresh state, the corpuscles will be found fused together and, under the influence of the pressure of a cover-glass, to undergo extraordinary changes in form and position. Any one acquainted with the remarkable photographs of Mitchell and Reichert illustrating the effects of venom upon red corpuscles will recognize the identity of the two pictures.

The description of agglutination of corpuscles by venom given by Mitchell and Reichert, and later by Mitchell and Stewart, in their papers on venom, and the studies upon venom recently conducted by Dr. Noguchi and myself, suggested a re-

study of the intravascular clotting of blood caused by venom injections. We were fortunate in having several kinds of venom with which to undertake this investigation. It has long been recognized that the venom of the viper family, to which our rattlesnake belongs, is especially prone to cause vascular clotting. Besides crotalus venom we have possessed other viper venoms—such as that of Russell's viper from India (*Daboia Russellii*) and *Trimere surus* from Japan. By far the most active venom in this respect is that of Russell's viper, as intravenous injections of it cause almost instantaneous 'clotting' of the blood in the right heart, pulmonary artery and vena cavæ. If these clots are removed immediately and examined (1) in the fresh state, and (2) after instantaneous hardening, no fibrin can be found. They consist exclusively of masses of agglutinated red corpuscles and are entirely free from evidences of clotting in the classical sense. But besides the change in adhesion of the corpuscles, still greater alterations of form and refraction have taken place in them; and sections of the 'clot' from the heart and in the vessels of the lung show extraordinary pictures of drawn and twisted bands of hyaline appearance which may readily be mistaken for modified fibrin.

These facts would seem to be of immense assistance in explaining the origin of certain thrombi met with in man in infections and other diseases, which are attended by marked blood destruction, and perhaps still other changes in the composition of the blood.

The light which the study of agglutinines has shed upon the general subject of thrombosis has served also to illuminate in no trifling way the path along which we are proceeding in gaining knowledge of certain forms of hæmorrhage. It is customary to ascribe hæmorrhages to two opposed conditions—to rupture of blood vessels and escape of blood corpuscles through the vessels by diapedesis. Only the second mode of origin needs enlightenment. Hitherto we have been obliged to be satisfied with a vague and hypothetical molecular alteration of the vascular wall as explaining the increased passage of red corpuscles into the tissues. It would now seem that at least certain forms of parenchymatous hæmorrhage are explicable in a more satisfactory and objective manner; and I will ask you kindly to turn your attention to this subject.

That no necessary relation exists between thrombosis and hæmorrhage can be shown experimentally by removing from rattlesnake venom its agglutinines for red corpuscles, when the hæmorrhage principle is left unaffected; and that no relation exists between hæmolysis and hæmorrhage can be inferred from the action of cobra venom which, while an active agent of blood destruction, causes but little hæmorrhage. But the entire independence of the principles which act injuriously upon blood vessels, and thus permit escape of blood, can also be shown by the use of ricin, which is non-hæmolytic, and which, in rabbits, produces extensive extravasation of corpuscles into the serous membranes.

Jacoby and Müller have shown that ricin is not robbed of its entire toxicity by digestion with artificial gastric juice, and Müller made the observation that the agglutinine is destroyed in the process. I found no trouble in confirming this finding of Müller, and in detecting that digested ricin is still capable of producing hæmorrhage.

If the thin mesentery of the rabbit is spread out and prepared and the capillaries lying within the hæmorrhagic areas are carefully studied, it will be seen that in neither venom nor ricin poisoning have

the red cells become fused and lost their independence, but the capillary walls have been injured in a definite and unmistakable manner. The extravasations take place not by diapedesis, as is now believed, but through actual rents in the walls. The explanation of the rents is of much interest. That they are not simple ruptures seems proved by the disappearance, as if through solution, of the parts of the walls at the site of the escape of corpuscles. The solution of continuity is one-sided, and in some instances is attended by a displacement of the adjacent endothelial cells, which are pushed outward, away from the vessel, by the force of the escaping blood. The escape of corpuscles by dissolution of the vascular walls is limited to capillaries and small veins. When acted upon by venom the vessels show irregular bulging of the walls, by ricin a localized dilatation or congestion of the vessels, which give rise to a glomerular appearance; but in a small number of places only does the extravasation occur. It is probable, therefore, that the points of injury to the vascular coat are many, but in a part only of these does the vessel give entirely away.

The existence, then, of a substance having an especial affinity for vascular endothelium may be considered as proved for snake venom and ricin. For this principle, if principle it be, we have proposed the name of hæmorrhagin, and we look upon it as a cytolysin for endothelial cells of blood vessels, the injury and destruction of which is the direct cause of the escape of blood into the surrounding tissues. It remains to be shown whether such hæmorrhagins are of common occurrence in nature, and to what extent they may play a part in animal pathology. I regard this as a most promising field of future exploration, for I conceive that bacteria and other pathogenic microorganisms probably produce endotheliolysins, and the action of hæmorrhagins may be the immediate cause of the extravasation of blood in purpuric states and some other forms of so-called parenchymatous hæmorrhage.

Should this view of the causation of hæmorrhage be supported by future studies we may well consider the possibility of preparing experimentally an antidotal agent for the principle involved in its production. We already have at hand certain observations bearing upon this question. You are all familiar with antivenin as prepared by Calmette and Fraser as an antidote to venom. Although contrary to the generally prevalent opinion, it may be affirmed that the value of the commercial antivenin is in inverse ratio to the hæmorrhage-producing power of the venom. This fact arises from the consideration that in the preparation of antivenin, cobra venom chiefly is employed, and it is almost devoid of the hæmorrhagic principle.

Venoms which cause much hæmorrhage exert a very destructive local effect upon the tissues. For this reason very little success has attended the efforts to produce an anti-toxin for viper venom. On this account, Dr. Noguchi and I have sought a means of modifying viper venom so as to remove the locally destructive effect and yet leave the value of the hæmorrhagic principle with which an immunity might be established. Through the use of hydrochloric acid we have succeeded in getting rid of the local effects, including the hæmorrhage, and yet have preserved the combining value of the hæmorrhagic principle, so that successive injections in animals of modified venom could be carried out. The serum of these animals contains an appreciable quantity of anti-hæmorrhagin as well as other antidotal principles, and is capable of neutralizing the local effects of rattlesnake venom.

That anti-hæmorrhagins, like other antitoxins, etc., could be produced experimentally must be inferred from Ehrlich's production of anti-ricin; for although he failed to distinguish between the hæmorrhagic and agglutinating principles in ricin, yet the neutralizing value of his anti-ricin seems to have included all the ricin principles.

If I have dealt somewhat fully with this topic it is, first, because of its importance to human medicine, and second, because in its light I must regard the outlook for a better understanding of a very obscure, serious and difficult pathological condition in man as of considerable brightness. Moreover, it may not be an Utopian dream, in view of what has already been gained, to look forward to the production of an antidote that, by neutralizing this poison for vascular endothelium, may provide a rational and certain therapeutic agent to combat this form of hæmorrhage.

I shall ask you to turn to another aspect of my theme, which relates to the occurrence, under natural conditions, of a whole host of cell-destroying—cellulicidal—substances in blood serum which, up to now, have received almost no attention, and which I regard as not without significance to human pathology. When one considers the diversity of agglutinines and solvents for blood corpuscles, bacteria and other cells contained in normal serum or open to experimental production, it will cause no great surprise to learn that the serum of warm- and cold-blooded animals contains corresponding active principles for kidney, liver and testicular cells. Dr. Noguchi and I have been engaged, during the past winter, in studying these cytotoxins, and have found them to have a wide distribution and to possess a considerable degree of activity.

In view of the ever-increasing number of activities with which almost daily discovery is endowing our body-fluids, the question of the independence and specificity of their constituent active principles has come to be an important one. In the studies under consideration we could show, by means of absorption test, that the agglutinines and solvents for blood, kidney, liver and testicular cells differ among themselves, and the removal of a part of them by means of certain of the cells does not prevent the action of the serum upon the remaining cells; from which it could be concluded that these principles are at least specially adapted to given cells. A general reduction in the activity of the serum which has lost a part of the solvents also suggests that they are not specific in the strictest sense.

It would carry us too far afield to discuss the different ways in which the manifold properties of serum may be explained; whether by supposing it to be a mine of diverse substances as rich as the endless activities which it exhibits, or whether its effects are produced by combinations and permutations among a smaller number of independent bodies. It is sufficient for the moment to have drawn attention to the multiplicity of the energies of serum in a relatively narrow circuit, in order that I may add a word upon what may not be an impossible form of activity, developed under pathological conditions, within the serum.

In speaking of blood destruction, I emphasized the absence from serum under normal states of cytolysins directed against its own cells, and took under consideration the pathological conditions under which a destructive property was apparent. Whether similar harmful properties for the organic cells are developed in serum has not been considered especially, but in view of the diverse activities of bacterial and other poisonous agents, they may well be

assumed to arise. But just as not all the forms of blood injury can be ascribed to the action of exogenic poisons, it is worth while inquiring whether any conditions may arise under which the injurious power of serum may be directed against its bodily organic cells.

You will not have failed to appreciate the dangerous nature of the forces inherent in serum, but fortunately for us these implements of destruction are not turned against ourselves. The protection which the body exercises against these weapons of offense is aptly described by Ehrlich as 'horror autotoxicus'—horror of self-poisoning. Were it conceivable that the body should be withdrawn, for an appreciable interval of time, from the operation of this restraining force we might, at any moment, be observed to run together and dissolve in our own juices! And yet, is it wholly without the realm of possible accidents that in respect to some organs and in some degree this 'horror' should be removed? I can not convince myself that in the progressively degenerative lesions of the body —those of the liver, kidney and brain, for example—where through years the process of destruction goes on, and where the reserve regenerative capacity normally present is held in check, that this 'horror' may not be in abeyance.

The many observations upon the effects of iso- and hetero-lysins—as for kidney and liver cells—about which there is no reasonable doubt, speaks, it seems to me, in favor of such a possibility. Dr. Pearce has studied through many months, in my laboratory, the action of nephrolysins, and has made observations of great importance with reference to experimental nephritis. The results of his studies will appear in due time, but I wish to refer to one fact brought out by his investigations that I think of especial interest.

A large part of the studies were made upon dogs, and by the way of preliminary observation, the urine was always examined before the experiment was begun. It was surprising to discover not infrequently albumen and casts in the urine of dogs apparently in the best of health; and on studying the kidneys, to find marked degeneration of the epithelium, and focal accumulations of cells of the plasma-cell type, such as occur in man in a definite form of non-suppurative interstitial nephritis.

The blood serum of normal dogs infused into other healthy dogs produces no symptoms nor disturbance of the renal function. But the serum of a dog with spontaneous nephritis gave rise to albuminuria and cast excretion, such as Dr. Pearce has observed in many instances of the infusion of the serum of the rabbit which had been treated previously with washed dog's kidneys.

That both iso- and hetero-nephrolysins set up the lesions of acute nephritis had been shown previously; but this observation of Dr. Pearce is of a different order. It must be considered either that some exogenic toxic agent set up the renal lesions in the first dog, and was present in the animal's blood in such quantity that, when its serum was infused in the second animal in the proportion of 1 to 500 of the body weight, it sufficed to produce marked disturbance of the renal function, such as is recognized in man as due to organic lesions; or that the degeneration of epithelium which may be assumed to exist in the first animal (which is still alive and under observation) provoked a series of changes with the production of toxic substances which for this animal are autotoxic and another animal of the same species isotoxic. It will not do to dogmatize about phenomena as complex as those we are now considering; but if the second view expressed

here is at all tenable, and it would seem to offer at least a rational explanation of the facts observed, we must admit the possibility, under pathological conditions, of the establishment of a vicious circle leading to progressive degeneration of organs, which could come into play only by the temporary suspension of 'horror autotoxicus.'

But I must turn from such baneful and, at present, perhaps, unprofitable speculations. The whole subject to which they refer represents a field of future exploration. That it is a territory not without fascination you will, I think, admit; and I am of the opinion that it is also a land of promise for the future of practical medicine.

The enormous advances made in the last decades in the study of the morphology of the cell are being paralleled by the gains in our knowledge of what may be called intracellular chemistry. This new knowledge is bearing the richest fruits, for among them are the newer conceptions of immunity, and of the physiological and pathological activities of a whole series of intracellular ferments.

Looked upon broadly, the corner-stone of modern pathology is toxicology. Without entering into a discussion of the general subject, I may remind you that while definite chemical poisons, such as arsenic, morphia, strychnia, etc., are capable of inflicting great injury upon different organic cells, their introduction in repeated feebly toxic doses into the body is not followed by a reaction the results of which are the appearance in the blood and elsewhere in the body of neutralizing and antidotal substances. The case is wholly different with a series of less definite, chemically speaking, toxic agents of which diphtheria and tetanus toxins, ricin and venom, and pathogenic bacteria and other cells are examples, for when introduced into the living body in this manner, they give rise to antitoxic and destructive substances to which the names antitoxin and cytolysin are being applied.

The precise manner in which these antagonistic bodies come to be produced is, for the present, purely speculation. But the lateral chain hypothesis of Ehrlich, which attempts to supply a graphic conception of the manner of their formation, has, whether expressing the truth or not, led to great advances in our knowledge. According to this hypothesis, the antitoxins, intermediary bodies, agglutinines, etc., are yielded by certain constituents of cellular protoplasm within the body, designated 'lateral or side chains' or 'receptors,' which combine with the protoplasmic constituents of body cells, bacteria or toxins used for immunization. This conjunction seems to injure or render useless the receptors of the cellular protoplasm without, at the same time, so seriously damaging the cell as to prevent regeneration. The regenerative process does not exactly restore the integrity of the cellular protoplasm, but, in keeping with the general law of regeneration enunciated by Weigert, there tends to be formed similar bodies in excess. The excessive or lateral chains, being useless to the cells in which they are produced, are cast off and appear in the body juices as intermediary bodies or 'ceptors,' which, according to their nature, are designated uniceptors (antitoxins, etc.) and amboceptors (intermediary bodies).

In antitoxic neutralization direct union between the toxin and antitoxin occurs; while in bacteriolysis and other forms of cytolysis there is conclusive evidence that, although the intermediary body unites first with the cells, this substance by itself can not bring about injury or solution, but after its union with the cells the substance called 'complement,' normally present in

the blood, is capable of being brought into action, whence the injury is inflicted. The action of the complement depends upon its possession of properties designated zymotoxic and toxophoric, through the influence of which hæmoglobin is set free from red corpuscles, various organic cells are dissolved, bacteria are disintegrated, and ciliar and flagellar motions are suppressed.

The intermediary bodies and complements upon which serum activity depends are contained within the blood; but there are certain kinds of natural poisons, of which venom is perhaps the best example, in which only the intermediary body occurs in the poison, the complement—the directly hurtful constituent—being supplied by the blood. I have already dwelt upon some of the principles of this poison, and I wish now to state briefly that venom possesses intermediary bodies capable of bringing into play complements which cause solution of many kinds of cells—those contained in nervous, renal, hepatic tissues and still other organs. All these solvents, as Dr. Noguchi and I have been able to show, possess a striking independence of action which can not fail to excite great wonder at the complexity of venom, and aid in the understanding of the elective affinities which poisons exhibit for certain organs, to which not only is disease of these organs to be attributed, but the selective action of remedies ascribed.

My purpose in bringing again to your attention the subject of venom intoxication is to present a remarkable instance of interaction of two substances, both of which are poisonous, but one of which is capable of affording protection from the other; a therapeutic paradox which is explicable upon the basis of the mechanism of immunity as formulated by Ehrlich.

I have referred to the cytolytic action of snake serum, and I wish now to tell you that the blood serum of the rattlesnake, moccasin and some other snakes is highly poisonous to warm-blooded animals. Dr. Noguchi and I have been able to show that the manner of action of the toxic principles of snake serum is comparable to that of venom, with, however, one very important difference. Both owe their poisonous action to intermediary bodies; but the one, that of venom, is able to attach the complement, necessary to complete the injurious system, of the animal poisoned; while the other, that of serum, can combine only with its own complement. While, therefore, venom is active even after heating to a relatively high temperature, serum is inactivated at the temperature (58° C.) at which its complement is destroyed. This temperature does not, however, affect the serum-intermediary body; and hence, while the heated serum is no longer toxic because it can not utilize a foreign complement, it is still able to unite, through its intermediary body, with cells for which it has affinity. This affinity is especially for nerve cells; and since the serum combines with the same lateral chains or receptors of the nerve cells that venom attacks, it is possible by using heated serum to prevent a later venom union. If, therefore, heated snake serum is injected into guinea-pigs they can be protected, for a time, from fatal cobra poisoning. The duration of this immunity is not great and its degree is not high; for, on the one hand, the normal metabolism of the cell modifies or destroys, sooner or later, the combined serum-intermediary body, and, on the other, an excess of venom can by mass action drive out the weaker serum constituents. This fact is brought readily into conformity with the belief that receptors are, after all, designed primarily, not as organs to be used under stress of pathological necessity, but

to serve the needs of physiological processes of nutrition.

Snake serum protection from venom had previously been observed by Phisalix and Bertrand, who endeavored to explain the phenomenon by supposing that antivenin was produced by the absorption of venom into the circulation of those animals. According to their view, the serum contains venom and antivenin; the first easily destroyed by heat, the second more resistant. Heating of the serum, while abolishing the venom activity, leaves that of the antivenin unimpaired, whence its protective action.

There is something highly artificial in this explanation, which agrees, moreover, very badly with the facts. First, venom is destroyed at a much higher temperature than antivenin; second, the toxin and antitoxin of venom, when brought together, whether in the circulation or in a test-tube, tend to combine and neutralize each other; and third, it is possible by replacement experiments *in vitro* to demonstrate the occupation of the receptors by the neurotoxin of serum and the consequent exclusion of the neurotoxic constituent of venom.

You will, I trust, pardon me for bringing before you a subject of such purely theoretical interest. My object in doing so is to indicate the aid which the chemical idea of cell and toxine unions is bringing into toxicology. But I shall not need to apologize deeply for this liberty, since in it may be detected a purpose in pointing the way along which pharmacology and later therapeutics may be conceived to pass.

We have now traversed a considerable territory and one not wholly free from rough places. But the commanding position which we have reached, and the breadth of view into the nature of pathological processes which has been secured, justify, I trust, the undertaking. But having proceeded so far, it were vain to turn back until we have examined another field just opened up to physiological and pathological investigation, at the entrance of which we stand.

That organs protected from decomposition tend to undergo solution by a process of self-digestion was first accurately shown by Salkowsky in 1882. Within the last two years, and chiefly through the labors of Jacoby and Conradi, interest in this subject has been revived, and a number of important facts, bearing upon physiological and pathological processes discovered. Autolysis, as the process is now called, has been studied from many different sides; the nature and the distribution of the active ferments; their multiplicity and specificity; their influence upon the coagulability of the blood, upon bacterial life, upon cellular degeneration under physiological conditions, and upon the resolution and absorption of pathological products, formations and exudates. These studies have already shown that in the intracellular ferments causing autolysis we possess a most important and potent series of agents which come into play under both physiological and pathological conditions.

All that is required to convince oneself of the phenomenon of autolysis is to place a portion of the liver or other organ, or a quantity of exudate, under conditions protected from decomposition and maintained at blood heat, when digestion will proceed. Care must be exercised to avoid using means of preventing putrefaction that may injure unduly the ferments. Two kinds of autolysis are now distinguished: (*a*) Antiseptic, in which it proceeds under chloroform or toluol, and (*b*) aseptic, in which the organs are exposed in a sterile condition. Manifestly only the first method is applicable to certain pathological products in which bacteria are present. As a result of this self-digestion, the coagulable al-

bumens are converted into non-coagulable proteid, and certain by-products, among them leucin and tyrosin, make their appearance.

Differences are noticeable in the readiness with which autolysis of organs takes place under different pathological conditions. Jacoby found that liver autolysis was much accelerated in animals poisoned with phosphorus; and I have made some tentative experiments upon the rapidity with which organs from infected and non-infected human beings undergo this change.

Many of you will have been impressed with the remarkable softness presented by the liver, spleen, kidneys and other organs in persons who have succumbed to typhoid fever, peritonitis, septicæmia, etc. This softness has nothing to do with putrefaction, and I think it reasonably certain that it is the result of autolytic processes which may have begun to operate even before death. The changes through which the acutely swollen spleen, such as is met with in typhoid fever, goes illustrate very well the manner of action of these ferments. The diffluent quality of the spleen in this disease quickly develops outside the body; and it can be shown to be independent of the post-mortem growth either of the typhoid bacilli or putrefactive bacilli. Every pathologist has seen a moderately firm spleen outside the body become soft and semifluid in a few hours; and I find that, reduced to pulp and placed under toluol-water, the same change takes place.

In view of the resemblance of the hepatic lesions of advanced phosphorous poisoning to those of the liver in acute yellow atrophy, and the frequency with which the latter obscure disease supervenes upon acute infections, and, further, in view of the close agreement of the chemical products of degeneration of liver tissue in yellow atrophy with those of autolysis of the liver, the question arises whether the hepatic lesions in acute atrophy may not be the result of active autolytic processes set up by some agent that is as yet unknown.

The alterations in structure and consistence of muscle occurring in certain acute diseases (such as the so-called Zenker's degeneration which appears in typhoid fever) have features in common with changes noted in autolysis. The softening and preparation for absorption of infarcted areas in the brain, kidneys, spleen and other organs are also attributable to the action of intracellular ferments; and a similar form of softening occurs, if imperfectly, in malignant tumors, notably carcinoma, and in syphilis, where ferment action is possibly accelerated through the use of drugs, of which potassium iodide is the most efficient in use.

On the other hand, not all dead tissues are subject to this digestive liquefaction and absorption. Tuberculous foci, though degenerated, are remarkably persistent; and, as Prudden has shown, undergo softening probably only when certain bacteria invade secondarily the necrotic areas. It is of importance, in this connection, to recall that streptococci, which in themselves are not energetic tissue dissolvers, bring about softening and cavity formation in tuberculous foci; and the question as to whether their action is a direct one through products of their growth, or an indirect one by causing an increase in autolytic ferments, is pertinent but not as yet to be answered.

Fresh pus obtained, let us say, from an empyema, or fresh sputum, kept under toluol at the body temperature, becomes fluid, and a creamy layer collects upon the surface. The cells and nuclei disappear, and there appears in the fluid, as Naunyn first ascertained in 1865, various distintegration products, among which are leu-

cin, tyrosin, xanthin, guanidin, etc. Pus which thus undergoes digestion is capable of dissolving fibrin and even portions of organs independent of the action of bacteria. From this the conclusion can be drawn that pus, or really the leucocytes of pus, possess active digestive properties, a fact which the history of abscess formation and the removal by leucocytes of necrotic and other kinds of tissue, renders easily comprehensible. Many years ago Weigert attempted to explain, by assuming the operation of a peculiar poison which prevented fibrin-formation, the absence of fibrin from abscesses, etc., in which the fibrin factors must have originally been present. It is much more probable that what happens is a digestive transformation of fibrinogen, or of fibrin at the moment of its formation, by the ferments of the pus cell.

Broadly speaking, exudates and necrotic tissue are removed in two ways: (1) by absorption, and (2) by organization. In the first mode disintegration and solution of the cells, etc., with the exception of the fat and certain other elements, such as pigment, take place, and an emulsion results well adapted for entrance into the lymphatics. In the second, new vessels develop and invade the exudate or necrotic tissue, and by supplying a fresh set of leucocytes to dispose of the offending material, it is finally removed. From what has already been said, the first series of changes will readily be recognized as caused by autolysis; but the operation of the same cause is not so apparent in the second series. And yet, the two series are essentially the same. In the one the original material contains ferments of a kind and a quantity sufficient to bring about the transformation which is necessary before absorption can take place; in the second, the ferments being originally insufficient, are renewed by fresh leucocytes which emigrate from the vessels, load themselves with débris, and finally accomplish their entire removal.

There is little doubt that in many pathological conditions the leucocyte is the essential agent in bringing about absorption; and what is required to accomplish this end is not living leucocytes so much as large numbers of these cells, since autolysis proceeds independently of the vitality, as such, of the cells. The fate of pathological formations is dependent in large part on the numbers of leucocytes present within them.

The different behavior of a caseous and croupous pneumonia; the facility with which the one and the difficulty with which the other undergoes resolution is to be ascribed probably in part to the absence in large measure of leucocytes from the tuberculous process and their presence in enormous numbers in the acute inflammatory condition. Other examples illustrating the importance of leucocytes in promoting autolysis and absorption might be given.

I have been interested for the past two years in studying autolysis of the exudate in the lung in two inflammatory conditions, namely, acute lobar pneumonia and unresolved pneumonia. The pathology of the latter condition, except so far as the organization of the exudate is concerned, is, as you know, involved in the deepest obscurity. The study of the histology of the lung in various stages of the process of organization emphasizes one pathological condition, the import of which appears great in view of our present knowledge of autolysis; the exudate in unresolved pneumonia is fibrinous rather than cellular, and many of the alveoli of the lung are filled with dense hyaline fibrinous masses. All attempts to explain upon ordinary etiological grounds the peculiar changes, or absence of changes, in unresolved pneumonia, have failed; and

evidently the peculiarity of the process is to be sought in other causes.

Friedrich Müller first studied autolysis of the lung in croupous pneumonia, and described in detail its occurrence and the chemical products, among which are lysin, leucin, tyrosin, purin bases and phosphoric acid, of the digestive process. I have found that it is in the stage of gray hepatization that autolysis takes place quickly and perfectly, while in the stage of red hepatization it is very imperfect—a fact that can, I think, be attributed to the small number of pus cells present in the latter condition. But if the lung in unresolved pneumonia is exposed to conditions favoring autolysis, the process is slow and incomplete as compared with what takes place in gray hepatization. In gray hepatization, autolysis after death is a mark of the tendency during life of the exudate to become absorbed; in unresolved pneumonia the absence or reduction of autolysis is equally an indication of the future fate of the exudate, namely, during life to undergo organization.

I am, therefore, inclined to view unresolved pneumonia as an acute lobar pneumonia in which the inflammatory exudate, either because of some disproportion between the leucocytes and other constituents, or other cause as yet unknown, failing to autolyze perfectly, can not be absorbed, and hence undergoes organization.

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SCIENTIFIC BOOKS.

A Revision of the Lepidopterous Family Sphingidæ. By the Hon. WALTER ROTHSCHILD, Ph.D., and KARL JORDAN, M.A.L., Ph.D. Novitates Zoologicæ, Vol. IX., Supplement. Issued at the Zoological Museum, Tring, April, 1903. Pp. cxxxv + 972; plates I–LXVII. 4to.

This great work, based upon the splendid collections contained in the museum at Tring, and also upon all the other large collections in Europe as well as those in America, which have been carefully consulted, has occupied the learned authors fully eight years in its preparation. It is truly *opus magnificum.* On every page it gives evidence of the most painstaking and minute research, and is the first really satisfactory attempt to collate and bring into systematic review what has been done during the past one hundred and fifty years in relation to the large and interesting family of insects with which it deals.

The work falls into three parts: The Introduction, covering one hundred and thirty-five pages; the descriptive portion, occupying eight hundred and thirteen pages; and a Synonymic Catalogue of the Sphingidæ of the World, to which one hundred and sixty-seven pages are allotted. Sixteen of the plates are devoted to figuring hitherto little-known or hitherto undescribed species. These plates are executed in photo-colortype, or by the half-tone process. The remaining fifty-one plates, which are beautifully engraved upon stone, are devoted to the illustration of anatomical details. Evidently neither labor nor expense has been spared in making the treatise one of the most satisfactory pieces of monographic work which have ever issued from the press.

The introduction has value not merely for the lepidopterist, but for all students of the biologic sciences, inasmuch as the laws and methods of procedure, which should govern in systematic work, are taken up and discussed at length. The statements which are made as to the principles of nomenclature are especially worthy of study, and the conclusions reached are such as undoubtedly command the respect and win the adherence of all those who are sufficiently well versed in this subject to appreciate the position taken by the authors.

The hawkmoths are divided into two great groups, the Sphingidæ Asemanophoræ, including the subfamilies Acherontiinæ and Ambulicinæ; and the Sphingidæ Semanophoræ, including the subfamilies Sesiinæ, Philampelinæ, and Chœrocampinæ. The 'law of priority' has been strictly applied in ascertaining the generic names, which should be used.